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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	PAPER NUMBER
1631	
MAIL DATE	DELIVERY MODE
02/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,954	GUSTAFSSON ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14,16,20-23,49-52,74-97 and 121-126* is/are pending in the application.

4a) Of the above claim(s) *4,12,16,20-23,49,81-83 and 91-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11,13,14,50-52,74-80,89,90,95-97 and 121-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/06/2008, 02/16/2007, 03/03/2006, 01/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-6,8-14,16,20-23,49-52, 74-97,121-126 are pending are pending.

Response to election of species requirement filed 01/05/2009 is acknowledged.

Applicant elected claims 13 and 89 for Groups D and E, respectively.

To summarize elections of species, the following elections have been made:

For Group A - Rule for step a) - a physico-chemical property of an amino acid at a position within a plurality of antibody sequences as set forth in claim 6.

For Group B - a descriptor of first value a substitution at a position in said plurality of positions represented by all or said portion of the variants (item i) in claim 8)

For Group C - a modeling step d), - computation of a generalized additive model as set forth in claim 11.

For Group D - type of further step performed in addition to the steps of claim 1 – redefining step as in claim 13

For Group E - a further step in step c) – assaying for reduction in virus as in claim 89,90.

Claims 4,12, 16,20-23,49,81-83,91-94 are withdrawn from consideration as directed to non-elected species.

Claims 1-3,5-11,13,14,50-52,74-80,89,90,95-97,121-126 are under consideration.

Claim Rejections - 35 USC § 102 and 103

2. Claims 1-3,5-11,13,14,50-52,74-80,89,90,95-97,121-126 are rejected under 35 U.S.C. 103(b) as unpatentable over Gustaffson et al (J. Mol. Recognition, 2001; 14:305-314; reference provided by applicant) and Peizi et al. (US 71717096) and further in view of Gustaffson et al (US 20040072245).

The instant claims are drawn to method for constructing a variant set for an antibody of interest. The method comprises the steps of creating a sequence space comprising one or more substitutions for positions of interest in the sequence of the antibody (selected using rules, such as accounting for physico-chemical properties, as in claim 6), measuring a property (such as reduction in viral index, per claim 89) for at least some variants, modeling sequence-activity relationship to generate values reflecting contribution of substitutions in the sequence to the measured property, based on these values redefining variant set and measuring property of variants arrived thereby.

Gustaffson reviews methods for exploration of sequence space for protein engineering and teaches that basic strategy for sequence-function search of sequence space is to identify starting sequence→ assay variants experimentally→ train

discriminate function, create related variants *in-silico*→ assay variants →select best variants. See Fig 2.

This reads on the method as claimed in general, without being limited to antibodies, or particulars of the discriminate function. With respect to the discriminate function, Gustaffson teaches that it can be any function that will generate a quantifiable value, such as neural network or principal component analysis, etc. See Fig 2.

There are multiple references teaching computational generation of antibody libraries.

Thus, Peizi et al. (US 71717096; priority date 11/28/2002) teach methods for designing antibody library. The method involves identifying the starter sequence of the antibody and variable positions of interest in its sequence, generating variants and sequence space, consecutive evaluation from sequence to structure to activity and choosing consensus variant profile that is likely to produce strong candidates in the functional screen.

Peizi et al. reference does not teach using scoring functions as in the instant method. However, as discussed in Gustaffson, any function that will generate a quantifiable value allowing to correlate sequence and function in the sequence-function search of variants can be utilized. One of ordinary skill in the art could have applied the known "improvement" technique discussed in Gustaffson in the same way to the method of Piezi and the results would have been predictable to one of ordinary skill in the art. Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR Int'l* 7, 127 S. Ct. at 1740.

Further, as described in Gustaffson et al (US 20040072245) protein sequence-function relationship can be determined using the method comprising the following steps[1]: receiving data characterizing a training set of systematically varied sequences of the target protein, wherein the data provides activity and sequence information for each protein variant in the training set; from the data, developing a sequence activity model that predicts activity as a function of amino acid residue type and corresponding position in the sequence; and using the sequence activity model to identify one or more amino acid residues at specific positions in the systematically varied sequences that are to be varied in order to impact the desired activity. See claim 1.

As Gustaffson, 2001, teach that any discriminate function that will generate a quantifiable value for sequence-function relationship can be used, it would be obvious that the method of Gustaffson et al (US 20040072245) can be utilized in the general method of Gustaffson, 2001 as applied to antibody variant generation in the method of Piezi.

With regard to claims 2,3, Gustaffson et al (US 20040072245) teach that the selection of variants may be repeated until the predicted fitness is exceeded. See Figs 6-7.

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[1] The method is nicely summarized in Fox et al reference (see IDS of 02/16/1997, reference C01):

1. Screen a small number of samples from associating sample activities with their sequences.
2. Build a statistical model that correlates the sequences with the measured activities.
3. Use the statistical model to identify residues that contribute most to improving the desired activity or fitness.
4. Build the next round library by incorporating residues that contribute most to the predicted fitness, rejecting those residues predicted to confer low fitness.

Iterate steps 1 through 4 to achieve higher fitness.

With regard to claims 4,5,124, Gustaffson et al (US 20040072245) teach that physicochemical properties can be used as the feature in correlating amino acids in amino acid positions in the polypeptide variants with the one or more desired properties. See paragraph [0157]:

> For example, if two polypeptide sequences are identical except for a single amino acid residue, and the sequences have different activities, then all difference in function is typically assumed to correlated only with that amino acid difference. Accordingly, essentially any way that the relative importance for a given variable towards a functional parameter Y can be scored is optionally used in these methods. To illustrate, the matrix is optionally based on regression-based algorithms, e.g., PLS, regression coefficients, VIP (Variable Importance for Projection)(one preferred algorithm), MLR (multiple linear regression), ILS (inverse least square), PCR (principal component regression), and/or the like. Additional alternatives include basing the loads matrix on pattern-based algorithms, such as neural networks, CART (classification and regression trees), MARS (multivariate adaptive regression splines), and/or the like. The methods also typically include sorting entries in the loads matrix, e.g., according to numerical value, etc.

With regard to claims 9,10,50-52, Gustaffson et al (US 20040072245) teach that various regression models can be used ([0102]-[0103]). In particular, partial least squares (PLS) algorithm is used. See p. 8-9.

With regard to claim 11, Gustaffson et al (US 20040072245) teach that various known techniques for generating models can be used, such as partial least squares, other regression techniques, as well as genetic programming optimization techniques, neural network techniques, recursive partitioning, and support vector machine techniques. Generally, the technique should produce a model that can distinguish residues that have a significant impact on activity from those that do not. Preferably, the model should also rank individual residues or residue positions based on their impact on activity. See [0102].

With regard to claims 75-80,89,90,122,123, if there are any differences between Applicant's claimed method and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach the various combinations of

selection particular antibodies, methods of testing their activity, or of selecting parameters in the known modeling algorithms, it would be conventional and within the skill of the art to select and/or determine such result-oriented variables. One of ordinary skill in the art would have been motivated to combine all known factors with no change in their respective functions, and the combination would have yielded nothing more than predictable results.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-6,8-14,16,20-23,49-52, 74-97,121-126 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. 2004/0072245 (co-pending application 10/379378) in view of Peizi et al. (US 71717096). The claims are directed to methods of for generating an optimized protein variant library, said method comprising: (a) receiving data characterizing a training set of a protein variant library, wherein protein variants in the library have systematically varied sequences, and wherein the data provides activity and sequence information for each protein variant in the training set; (b) from the data, developing a sequence activity model that predicts activity as a function of amino acid residue type and corresponding position in the sequence; (c) using the sequence activity model to select one or more amino acid residues at specific positions in the systematically varied sequences that are predicted to provide desired activity; (d) generating an optimized protein variant library, wherein the sequences of the members of the optimized protein variant library each comprise the one or more selected amino acid residues.

Although the claims are not directed to generating an optimized variant library of antibodies, generating such optimized libraries for antibodies is well known in the art – see Peizi et al. (US 71717096), for example, and it would be obvious to apply the method of 2004/0072245 to generate variants of antibodies.

This is a provisional obviousness-type double patenting rejection.

4. Similarly, claims 1-6,8-14,16,20-23,49-52, 74-97,121-126 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-102 of co-pending application 10/874802 in view of Peizi et al. (US 71717096). The rejection is applied for essentially the same reasons, as the claims of 10/874802 are similar to the claims of 10/379378 addressed above[2].

Prior art made of record

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Schneider et al. ("Peptide design by artificial neural networks and computer-based evolutionary," Biochemistry, Vol. 95, Issue 21,pages 12179-12184; IDS of 03/03/2006, reference C01) teach a method for peptide design by artificial neural networks comprising the steps of identification of a "seed peptide" with a desired activity, generation of variants selected from a physicochemical space around the seed peptide, modeling of a quantitative sequence-activity relationship by an artificial neural network.

Koshi et al (PROTEINS: Structure, Function. and Genetics 27:336-344, 1997) teach utilizing of physicochemical properties in structure-function mapping of residues of antibodies.

Conclusion

6. No claims are allowed

[2] A large family of related applications is noted.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631

mlb